REMARKS

Claims 1-4, 6, 9-12, 14, and 23-27 are currently pending in the present application. By virtue of this response, claim 27 has been cancelled, and claims 1 and 9 have been amended. Support for the amendment to claims 1 and 9 can be found in the specification at least at page 10, lines 19-23 and page 22, lines 8-19. Accordingly, claims 1-4, 6, 9-12, 14, and 23-26 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

Information Disclosure Statement

Applicants acknowledge that the Information Disclosure Statement submitted on July 24, 2006 is in compliance with the provisions of 37 CFR 1.97 and has been considered by the examiner.

Claim Rejections Under 35 U.S.C. 112, First Paragraph

Claims 1-3, 6, 9-11, 14, and 23-27 stand rejected under 35 U.S.C. 112, first paragraph allegedly because the specification, while being enabling for methods of treating or delaying HPV associated lesions through administration of the ISS sequence of SEQ ID NO: 1, does not reasonably provide enablement for methods of doing so in any mammal wherein the ISS comprises either SEQ ID NO: 1 or any of the sequences within the scope of (e.g.) claims 1-3. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Preliminarily, Applicants respectfully point out that the examiner may have misread claim 1 and claim 9. As shown below, Claim 1 and claim 9 each recite that the mammal is human. Current claim 1 recites:

> A method of delaying development of a lesion associated with papillomavirus infection in a mammal who has been exposed to papillomavirus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) to said mammal, wherein the ISS comprises the sequence 5'-C, G, pyrimidine, pyrimidine, C, G-3', wherein the polynucleotide is at least 8 and less than about 200 nucleotides in length, wherein the mammal is a human, and the

papillomavirus is human papillomavirus (HPV),wherein a papillomavirus antigen is not administered in conjunction with administration of said composition, wherein said composition is administered at a site of exposure to papillomavirus, and wherein said composition is administered in an amount sufficient to delay development of a lesion associated with papillomavirus infection. (emphasis added)

Current claim 9 recites:

A method of reducing severity of a lesion associated with papillomavirus infection in a mammal infected with papillomavirus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) to said mammal, wherein the ISS comprises the sequence
5'-C, G, pyrimidine, pyrimidine, C, G-3', wherein the polynucleotide is at least 8 and less than about 200 nucleotides in length, wherein the mammal is a human, and the papillomavirus is human papillomavirus (HPV), wherein a papillomavirus antigen is not administered in conjunction with administration of said composition, wherein said composition is administered at a papillomavirus-associated lesion, and wherein said composition is administered in an amount sufficient to reduce severity of a lesion associated with papillomavirus infection. (emphasis added)

The Examiner states at page 2 of the Office Action that the specification is enabling for methods of treating or delaying HPV associated lesions through administration of the ISS of SEQ ID NO:1.

Applicants traverse this rejection of claims. The specification provides adequate guidance to enable the claims in accordance with 35 U.S.C. §112, first paragraph.

The Examiner has not established a prima facie case for lack of enablement.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' . . . Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). With respect to the enablement requirement for patentability, the burden is on the Examiner to show that the specification is not enabling. MPEP § 2164.04 states that "[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject

matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." The MPEP cites the decision in *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971), in which the court stated that the Patent Office, when making a rejection on the basis of nonenablement, must explain why it doubts the truth or accuracy of the disclosure by backing up its assertion with acceptable contrary evidence or reasoning.

The Examiner has failed to meet the burden of showing that the specification does not provide an enabling disclosure. Applicants respectfully submit that the specification provides all the information required for one of skill in the art to make and use the invention to delay development of a lesion associated with papillomavirus infection in a mammal who has been exposed to papillomavirus, or reduce the severity of a lesion associated with papillomavirus infection in a mammal infected with papillomavirus, as claimed.

The specification teaches how to make the claimed polynucleotides comprising an ISS. The specification teaches the requirements for the ISS. See page 21, line 21 through page 24, line 18. The specification teaches how to synthesize ISS. See page 25, lines 8-23 and page 26, line 10 through page 27, line 8. The specification describes how to assay for delaying development of a viral infection. See, for example, page 15, lines 15-21. The specification states that "ISS have been described in the art and *may be readily identified using standard assays* which indicate various aspects of the immune response, such as cytokine secretion, antibody production, NK cell activation and T cell proliferation." Page 21, lines 13-20, emphasis added. The specification provides a number of references that describe ISS. See pages 4-7.

On page 21, line 21 through page 22, line 5, the specification teaches that "[t]he ISS can be of any length greater than 6 bases or base pairs and generally comprises the sequence 5'-cytosine, guanine-3', preferably greater than 15 bases or base pairs, more preferably greater than 20 bases or base pairs in length. As is well-known in the art, the cytosine of the 5'-cytosine, guanine-3' sequence is unmethylated. An ISS may also comprise the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3'. An ISS may also comprise the sequence 5'-purine, purine, C, G,

pyrimidine, pyrimidine, C, C-3'. As indicated in polynucleotide sequences below, an ISS may comprise (*i.e.*, contain one or more of) the sequence 5'-T, C, G-3'. In some embodiments, an ISS may comprise the sequence 5'-C, G, pyrimidine, pyrimidine, C, G-3' (such as 5'-CGTTCG-3'). In some embodiments, an ISS may comprise the sequence 5'-C, G, pyrimidine, pyrimidine, C, G, purine, purine-3'. In some embodiments, an ISS comprises the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine-3' (such as 5'-AACGTT-3'). In some embodiments, an ISS may comprise the sequence 5'-purine, T, C, G, pyrimidine, pyrimidine-3'." Furthermore, the specification teaches approximately 170 specific ISSs. See pages 22-24.

The specification teaches that "[t]he ISS *can be synthesized using techniques and nucleic acid synthesis equipment which are well known in the art* including, but not limited to, enzymatic methods, chemical methods, and the degradation of larger oligonucleotide sequences. See, for example, Ausubel et al. (1987); and Sambrook et al. (1989)." Page 25, lines 8-15, emphasis added. Synthesis of an ISS would be routine in the art.

The specification teaches methods for assessing symptoms of papillomavirus infection. The specification teaches that "[t]he exact form of prevention, palliation or improvement will depend on the particular *papillomavirinae* type and the symptoms experienced by the individual but includes reduction in size and/or duration of lesions and/or warts, reduction in symptoms of papillomavirus infection or reduction in frequency or number of recurrent lesions. In some embodiments, administration of an ISS-containing polynucleotide results in a reduction in viral titer (a reduction of which indicates suppression of viral infection). In other embodiments, the number of warts is reduced. In other embodiments, viral infection is suppressed, which may be indicated by any one or more of a number of parameters, including, but not limited to, extent of one or more symptoms and viral titer. In other embodiments, recurrence, which is generally indicated by appearance of one or more symptoms associated with infection, is reduced." Viral titer may be assessed in biological samples using standard methods known in the art. Page 39, line 6 through page 41, line 4.

The specification teaches sequence requirements for ISS, provides specific examples of ISS, and provides information regarding how to identify and evaluate other ISS using techniques that are well known in the art. Synthesis of ISS may also be achieved using techniques that are described in the specification and are standard in the art. Thus, the specification provides adequate guidance regarding how to make ISS.

The specification teaches how to use the claimed ISS. The specification provides guidance regarding administration of the claimed compositions. For example, see the specification beginning at page 34. Suitable formulations and routes for administration are disclosed at least at page 34, line 23 through page 38, line 2. In addition, the specification provides working examples. Although working examples are not required for enablement (MPEP §2164.02), the claimed invention is exemplified in Examples 1-2 provided on pages 43 to 45 of the specification. These examples demonstrate that 1) in the canine oral papillomavirus model, and under the conditions described in Example 1, injection of ISS in the papillomas when papillomas first appear appears to enhance the time of lesion regression as compared to the time of spontaneous lesion regression; and 2) in the cutaneous papillomatosis in a rabbit model, and under the conditions described in Example 2, treatment Group C demonstrated a reduction in the size of the ISS treated papillomas compared to untreated papillomas. Thus, in two different animal models, and under the conditions described for each model, the administration of an illustrative ISS, SEQ ID NO:1 (which comprises a "TCG"),[1] was effective at enhancing the time of lesion regression (canine model) or reducing the size of the ISS treated papillomas compared to untreated papillomas (rabbit model).[2]

It would not require undue experimentation to make and use the claimed invention.

As discussed above, the specification provides guidance regarding *how to make* ISS as claimed. Such techniques are standard in the art. Moreover, sequence requirements for ISS are set forth in the specification, as well as approximately 170 examples of specific ISS polynucleotide

[1] At page 4 of this Office Action, the Examiner indicates that the reference Fearon teaches that ISS sequences wherein the TCG is found in the ultimate or penultimate residues were inactive. This issue is further addressed at pages 13-14 of this amendment.

[2] At page 4 of the Office Action, the Examiner states "[t]he application shows that the sequence of SEQ ID NO:1 is effective in mice." (emphasis added) Applicants point out that the specification describes canine and rabbit models of papillomavirus in Examples 1 and 2.

sequences, and methods for identifying and testing additional ISS are described in the specification and are well known and available in the scientific literature. Methods for *how to use* ISS and for practicing the claimed methods are described in detail in the specification, in terms of formulations and routes of administration, as well as testing for modulation of an immune response, using standard techniques in the art. In addition, working examples are provided as described above. For a *prima facie* case of non-enablement, the burden is on the Office to demonstrate that there is a reasonable basis to question, the presumptively sufficient disclosure made by the applicant. *See*, for example, *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Applicants respectfully submit that the Examiner has not produced adequate evidence to support a lack of enablement, *i.e.*, to establish that with the teachings provided in the specification, a person skilled in the art could not determine that the development of a lesion associated with papillomavirus infection has been delayed in a human who has been exposed to papillomavirus or the severity of a lesion associated with papillomavirus infection has been reduced in a human infected with papillomavirus.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Applicants submit that in the instant case, enablement is provided by the disclosure in the specification, and also by knowledge in the art about ISS polynucleotides. In addition to the guidance provided by the specification, immunostimulatory polynucleotides are well known in the art and polynucleotides with immunostimulatory sequences active in cells of many mammalian species have been described in the scientific literature, including humans, monkeys, chimpanzees, cows, swine, dogs, cats, rabbits, mice, and rats. In particular, much has been described about ISS activity in human cells and immunostimulatory sequences active in human cells have been the subject of much scientific and patent literature. It would not require undue experimentation to apply the foundation provided by the ISS art, in combination with the teachings of the specification, to identify ISS sequences that will be useful in the practice of the claimed invention.

The court found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents

working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). As discussed above, the specification provides direction and guidance on how to practice the invention and presents working examples. Additionally, in view of the fact that much has been described about ISS activity in human cells and immunostimulatory sequences active in human cells have been the subject of much scientific and patent literature, Applicants submit that there was a high level of skill in the art regarding ISS technology.

The court in *United States v. Telectronics.* held that "[s]ince one embodiment [was] . . . disclosed in the specification, along with the general manner in which its current range was ascertained, . . . other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 786 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). The Federal Circuit has stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Applicants respectfully submit that the specification provides a reasonable amount of guidance to the skilled artisan with respect to the direction in which the experimentation should proceed to optimize the teachings of the specification and the art and that any additional experimentation is well within the level of ordinary skill in the art, *i.e.*, no *undue* experimentation is required. Applicants respectfully submit that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity by methods known in the art and disclosed in the specification, including in the animal models described in Examples 1 and 2, are well within the bounds of routine experimentation by one of skill in the art.

Therefore, given the guidance in the specification and in view of the working examples, it would not require undue experimentation for a skilled artisan to practice the claimed invention. Applicants respectfully submit that the pending claims are in compliance with the enablement requirement and that the Examiner has not established a *prima facie* case for lack of enablement.

At page 3 of the Office Action, the Examiner states that "[i]n the present case, the claims are broadly drawn to the use of any oligonucleotide sequence (or of any sequence of between 6 and

200 bases in length) comprising the ISS sequences disclosed in the claims for the treatment or delaying of lesions associated with human papillomavirus (HPV) infection. In support of the claimed invention, the application has shown that the administration of the sequence of SEQ ID NO:1 (22 bases in length) was effective for the claimed purposes."

The claims do not recite "treatment or delaying of lesions associated with HPV" as the Examiner contends. The claims recite, in part, delaying development of a lesion associated with papillomavirus infection in a mammal (wherein the mammal is a human) who has been exposed to papillomavirus (claim 1) and reducing severity of a lesion associated with papillomavirus infection in a mammal (wherein the mammal is a human) infected with papillomavirus (claim 9). Lesions of papillomavirus are known in the art and described in the specification at least at page 14, lines 18-24. The Examiner states that the application has shown that the administration of an illustrative ISS, that is, the ISS shown in SEQ ID NO:1, was effective for the claimed purposes. The Examiner states that the application does not demonstrate that any sequence comprising the sequences in claims 1-3, or sequences consisting of such sequences would also be so effective. Applicants disagree. First of all, a specific level of efficacy, including clinical efficacy, as relates to a claim, is not required for compliance with Section 112, first paragraph, enablement. Secondly, SEQ ID NO:1, which the Examiner acknowledges in the Office Action at page 4 "is effective in mice"[3] is comprised of the sequence recited in Claim 1, that is 5'-C,G, pyrimidine, pyrimidine, C,G-3' (SEQ ID NO:1: 5'-TGACTGTGAACGTTCGAGATGA-3'); comprised of the sequence recited in Claim 2 (SEQ ID NO:1: 5'-TGACTGTGAACGTTCGAGATGA-3'); and comprised of one of the sequences recited in claim 3 (SEQ ID NO:1: 5'-TGACTGTGAACGTTCGAGATGA-3'). In fact, contrary to the Examiner's statement, the application does demonstrate that a sequence comprising the ISS recited in claim 1 and claim 2 and one of the ISS sequences recited in claim 3 is effective in the animal models disclosed in the Examples. Furthermore, Applicants submit that the possibility that the invention may not work in every species encompassed by a claim does not necessarily render the claim nonenabled, because a claim may encompass inoperative embodiments. MPEP § 2164.08(b). In *Atlas Powder Co. v. DuPont*, 750 F.2d 1569, 1576 (Fed. Cir. 1984), the court stated

that "[i]t is not a function of the claims to specifically exclude . . . possible inoperative substances." Further, the MPEP states that "[t]he standard [for enablement] is whether a skilled person could determine which embodiments. . . would be inoperative or operative *with the expenditure of no more effort than is normally required in the art.*" MPEP 2164.08(b), emphasis added. In *Atlas Powder* forty percent of about 300 experiments performed by the appellee failed for one reason or another. However, the Federal Circuit upheld the lower court's finding that the experiments were designated as failures because they were not optimal under all conditions, and held that optimality is not required because one skilled in the art would know how to modify those failures to achieve a better result. As discussed above, a great deal of guidance is provided by both the specification and the knowledge in the art as to the claimed invention.

The Examiner states at page 4 of the Office Action that the art teaches that "there have been no published reports of ISS activity in human cells by" ISS sequences of less than 8 nucleotides in length and refers to Fearon et al. The Examiner references Verthelyi et al. as indicating that the minimum length for a cytokine stimulating ISS is about 18 bases. Without acquiescing to this rejection and solely in an effort to expedite prosecution, Applicants have amended claim 1 and 9 to recite that the polynucleotide comprising an ISS is at least 8 and less than about 200 nucleotides in length. With respect to Verthelyi et al., Applicants invite the Examiner's attention to Verthelyi et al. pages 2373 which states that the minimum length of an active D ODN is about 18 bp. Verthelyi et al. pages 2373 to 2374 indicate that an active D ODN has the sequence PuPyCGPuPy, which is distinguished from the claimed invention that recites, in part, that the ISS comprises the sequence: 5'-C, G, pyrimidine, pyrimidine, C, G-3'. Therefore, the Verthelyi et al. statement regarding the minimum length of a D ODN is not applicable to all ISS and does not apply to the presently claimed invention.

The Examiner states at page 4 of the Office Action that Fearon "also teaches that ISS sequences wherein the sequence TCG is found in the ultimate or penultimate residues, such as in the

[3] As stated above, Examples 1-2 describe canine and rabbit animal models. Applicants believe the Examiner may have made an inadvertent error in referencing "mice" and may have intended to reference canine and rabbit animal models shown in Examples 1-2.

case of the sequences of each of claims 1-3, of the sequence were also inactive. As discussed above, "TCG" is found in SEQ ID NO:1, which is comprised of the sequences recited in claim 1, claim 2 and one sequence recited in claim 3, and the Examiner has acknowledged that SEQ ID NO:1 was effective in the mice.[4]

The Examiner references Fearon et al. as teaching that structural requirements must be met to ensure active ISS sequences, and that the nature of the bases outside of a hexamer is also important for activity. The Examiner also references Marshall et al. as teaching that different ISS have different immunomodulating activities. None of these references support a finding of non-enablement, because it would not require undue experimentation to make and use the claimed invention. Whether or not different ISS have different immunomodulating activities, and whether or not certain ISS structural requirements may affect activity, if one of skill in the art can make and use the claimed invention based on the disclosure in the specification coupled with knowledge known in the art, without resorting to undue experimentation, the claimed invention is enabled. It would not require undue experimentation to make and use the claimed invention. The Examiner states that Verthelyi, et al., states that humans respond poorly to the optimal ISS sequences of mice. Compliance with Section 112, first paragraph does not require optimizing ISS sequences. The fact that there may be different ISS that have different activities in different mammals does not render the claimed invention non-enabled. In *In re Wands*, the court held that the enablement requirement was satisfied even though only 4 of 9 antibodies analyzed (44%) were found to have the claimed binding requirements and those successful 4 were produced in only 2 of 10 fusion experiments. *In re Wands*, 858 F.2d 731, 783-39 (Fed. Cir. 1988).

An analysis of the factors set forth in In re Wands shows that the claimed invention is enabled.

[4] As stated above, Examples 1-2 describe canine and rabbit animal models. Applicants believe the Examiner may have made an inadvertent error in referencing "mice" and may have intended to reference canine and rabbit animal models shown in Examples 1-2.

As set forth in *In re Wands*, 858 F.2d 731,737 (Fed. Cir. 1988), several factors must be weighed in an enablement analysis. These factors include: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The MPEP states that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." The factors must all be considered in an enablement analysis; no one factor is dispositive. Applicants therefore provide the following enablement analysis using the factors set forth in *In re Wands*:

A. With respect to the breadth of the claims, the claims are directed to methods for delaying development of a lesion associated with papillomavirus infection in a mammal (wherein the mammal is a human) who has been exposed to papillomavirus (claim 1) and reducing severity of a lesion associated with papillomavirus infection in a mammal (wherein the mammal is a human) infected with papillomavirus (claim 9). ISS are well known in the art and may be identified and tested using techniques that are well-established in the art.

B. With regard to the nature of the invention, the invention relates to methods for delaying development of a lesion associated with papillomavirus infection in a mammal who has been exposed to papillomavirus (claim 1) and reducing severity of a lesion associated with papillomavirus infection in a mammal infected with papillomavirus (claim 9). Methods for assessing delaying development of a lesion associated with papillomavirus and reducing severity of a lesion associated with papillomavirus are disclosed in the specification and are well known in the art. Furthermore, working examples are provided which exemplify the claimed methods.

C and D. As discussed above, the state of the prior art (factor C) and the level of one of ordinary skill (factor D) are high, because much has been written in both the scientific and patent literature about how to make and use ISS in several species.

E. With regard to the level of predictability in the art, it is predictable that many sequences within the parameters set forth in the specification are operable in the claimed invention,

as demonstrated by the working examples in the specification. The fact that the activity of a polynucleotide may be fine-tuned or optimized by sequence adjustments does not indicate unpredictability or a lack of enablement.

F and G. With respect to the amount of direction provided by the inventor (factor F) and the existence of working examples (factor G), Applicants disclosed working examples in the specification, showing that the methods of the invention work as claimed, and guidance is provided in the specification regarding how to identify and assess additional ISS polynucleotide for use in the claimed methods.

H. With respect to the quantity of experimentation needed to make or use the invention based on the content of the disclosure, a number of examples of ISS polynucleotides are provided in the specification, including one which is exemplified in the claimed method in the working examples, as well as disclosure teaching how to identify and evaluate other ISS. Further, numerous ISS are known in the art, as well as techniques to test them for immunostimulatory activity, for which references are provided in the specification and incorporated by reference (pages 5-7).

In conclusion and in view of the foregoing, the amount of experimentation needed to practice the claimed invention or make the claimed compositions is not undue. Applicants submit that the presently claimed invention is in full compliance with Section 112, first paragraph, and request withdrawal of this rejection of claims.

Claim Rejections Under 35 U.S.C. §103(a)

Claims 1-4, 6, 9-12, 14, and 23-26 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Beutner, Bauman, and Yamamoto, and further in view of either of Raz et al. (U.S. Patent 6,514,948), and Schwartz et al. (WO 98/88795- of record in the Feb 2002 IDS).

Applicants traverse this rejection.

Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. A *prima facie* case of obviousness requires that three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion of motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); MPEP §2143. All three elements of a *prima facie* case must be present in order for the Office to meet its burden. None of these three criteria for obviousness is satisfied by the currently cited references. Furthermore, in determining obviousness, Section 103 expressly requires considering the claimed invention "as a whole". The properties and advantages of the invention are part of the invention as a whole.

Applicants remind the Examiner that the core references cited to support this Section 103 rejection of claims (that is, *Beutner, Bauman, Yamamoto,*) were previously found to be insufficient to support a Section 103 rejection of claims (See Office Action in this application mailed December 16, 2004, at page 5, withdrawing this rejection). In that Office Action, the Examiner states that Applicant's argument that references do not teach the use of ISS sequences identified in the claims was persuasive. In the current Office Action, the Examiner states at page 6 that he agrees that no one of the cited references provides sufficient teachings to render the claimed invention obvious. Applicants also believe that the references cited by the Examiner do not teach or suggest all the claim limitations. Yet, in the current Office Action, the Examiner maintains the Section 103 rejection based on these same core references. None of the core references, Beutner, Bauman, or Yamamoto, alone or together, teach or suggest the use of an ISS for delaying the development of or reducing the severity of a lesion associated with papillomavirus infection, wherein the composition comprising the ISS is administered at a site of exposure to papillomavirus, or at a papillomavirus-associated lesion, respectively, and wherein papillomavirus antigen is not administered in

conjunction with. The secondary references, Raz and Schwartz, do not cure the deficiencies of the core references.

In the current Office Action at page 6, the Examiner states that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. The Examiner alleges that each of the arguments provided by Applicants fail to consider the teachings of at least one of the references. Applicants disagree with this allegation by the Examiner. Furthermore, Applicants believe that the Examiner has not considered the invention as a whole.

Bauman teaches administration of interferon-α ("IFN-α") as a supplement to surgical removal of human papillomavirus ("HPV") lesions. Administration of any therapeutic substance as a supplement to surgical therapy would necessarily be at a site *other than a lesion* (as such lesion would have been removed) or a site of exposure to a papillomavirus. Beutner teaches administration of imiquimod, for treatment of genital warts. Imiquimod is disclosed by Beutner as inducing IFN-α as well as "a variety of cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)." Beutner, page 231. Beutner also states that "[i]n human peripheral blood mononuclear cells, imiquimod induces IFN-α, IL-1, and TNF-α, but not IL-2. Human keratinocytes exposed to imiquimod demonstrate an increase in messenger RNA for IL-1, IL-6, and IL-8. *Which of these cytokines accounts for the clinical response is not yet known.*" Beutner, page 237, emphasis added. Yamamoto teaches the ability of oligonucleotides to induce IFN-α, -β, and -γ in peripheral blood lymphocytes *in vitro*. Yamamoto discusses oligonucleotide induced production of interferon in the context of antitumor activity, but *does not teach or suggest the use of ISS as a treatment of a viral infection*.

The Examiner alleges that Applicants have not based traversal arguments on the combination of references. The Examiner states that Bauman does not teach the use of ISS in any capacity. Applicants believe that modifying Bauman in order to combine the teachings of Bauman with Beutner or Yamamoto would destroy the intended function of Bauman, that is, administration

of IFN-α as an adjunct therapy to surgical excision. Furthermore, taking into consideration the claimed invention as a whole, Bauman would not suggest administration of IFN-α to the site of a papillomavirus lesion or site of exposure to papillomavirus to one of skill in the art because there is no lesion present. It has been surgically removed. Bauman would suggest to one of skill in the art that IFN-α could not be used alone to treat HPV. Yamamoto discusses induced production of interferon in the context of antitumor activity. The Examiner's modification of Yamamoto, in order to combine Yamamoto with Bauman and Beutner, destroys the intended function of Yamamoto, that is, antitumor activity. Applicants submit that there would be no motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or to combine reference teachings, especially when modifying a reference destroys its function.

In relying on the combination of Bauman, Beutner and Yamamoto, the Examiner appears to be alleging that their teachings regarding therapies (INF-α with surgery, imiquimod, and oligonucleotides) are equivalents that can be interchanged. There is no reasonable expectation that a cytokine inducer, such as the imidazoquinoline imiquimod (Beutner), an oligonuleotide (that is suggested by Yamamoto to be used in an antitumor context) and IFN-α used in combination with surgery for the treatment of papillomavirus (Bauman), would function equivalently in the treatment of any viral infection, including papillomavirus. Bauman's teaching of IFN-α as an adjuvant therapy to surgery (among a disclosure of other therapies), Beutner's teaching of the use of imiquimod for genital warts, and Yamamoto's teaching of the use of oligonucleotides for in vitro antitumor activity are far enough removed from one another that motivation to modify them in order to combine teachings can only be found in the Examiner's impermissible use of hindsight reconstruction. Even if the references are combined, one of skill in the art would not arrive at the presently claimed invention. The Examiner's reliance on Raz and Schwartz to cure the deficiencies of the core references is misplaced. Raz does not teach administration of an ISS at the site of exposure to papillomavirus or at the site of a lesion as claimed. Raz teaches administration of an ISS prior to exposure to an antigen, versus the claimed methods that require administration after exposure, that is, at a site of exposure or at the site of a lesion. Schwartz does not teach

administration of an ISS at the site of exposure to papillomavirus or at the site of a lesion as claimed, much less in the absence of papillomavirus antigen as claimed. The Examiner has had to resort to the use of a combination of five references, selectively picking and choosing from among their teachings, including, for some of the references, in a way that destroys their disclosed function, in order to maintain a Section 103 rejection of claims. There is no motivation to combine the teachings of Bauman, Beutner and Yamamoto, and Raz and Schwartz do not cure the deficiencies of Bauman, Beutner and Yamamoto.

Furthermore, nothing in the cited references or the knowledge in the art at the time of filing, would have provided a skilled artisan with a reasonable expectation of success in practicing the claimed invention, as required for a *prima facie* case for obviousness.

It is a threshold requirement that all limitations be present in the cited references before it is even relevant whether there was a reasonable expectation of success by one of ordinary skill in the art. In the present case, the cited references do not disclose all of the elements of the claimed invention, either singly or in combination. Therefore, there could have been no reasonable expectation of success, since one of skill in the art could not have discerned each and every limitation of the claimed invention in the cited references.

Applicants provided information (press releases) to the Examiner in the Office Action mailed November 17, 2005, regarding the suspension of Eli Lilly and 3M Phase III clinical trials of resiquimod (reported to induce cytokines, including IFN-α) for the potential treatment of herpes simplex virus (HSV) due to a showing of inadequate efficacy. The Examiner did not address this submitted information in the instant Office Action. The Examiner stated to Applicants' representative in the telephone call of October 18, 2006, that this information is allegedly not relevant to the currently claimed methods. Applicants disagree with this allegation. Imiquimod and resiquimod are both from the imidazoquinoline family and are known to induce cytokine secretion. See, for example, Dockrell et al. (2001, Journal of Antimicrobial Chemotherapy 48:751-755), attached hereto as Exhibit 1. Applicants believe that this information related to resiquimod failures is relevant to the claimed invention. In Phase III clinical trials, a cytokine inducer of the imidazoquinoline family failed to show clinical efficacy, thus providing objective evidence of non-

obviousness of the claimed invention. There is no reasonable expectation of successfully arriving at the claimed invention based on the combination of references used by the Examiner, especially in view of the press release on failure of an imidazoquinoline to show clinical efficacy in a Phase III trial of viral infection.

In summary, the references cited by the Examiner do not teach or suggest all the claim limitations. There is no motivation to modify the references in order to combine them, and even if combined, they do not provide a reasonable expectation of success with respect to the claimed invention at the time of filing. When the invention is viewed as a whole, this obviousness rejection must fail as a matter of law. Furthermore, Applicants show evidence of failure of others using a cytokine inducer in the same family as imiquimod, in a Phase III clinical trial of human viral infection. In view of the arguments and evidence above, Applicants request withdrawal of this Section 103 rejection of claims.

Double Patenting

Claims 9-12, 14, 25, and 27 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 11 of copending Application No. 10/898,512. As this is a provisional rejection, Applicants would like to address this rejection when otherwise allowable subject matter is determined.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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Review

Imiquimod and resiquimod as novel immunomodulators

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Augmenting the host's natural immune response to viruses by the administration of exogenous cytokines such as interferon-α (IFN-α) is a strategy increasingly employed in antiviral therapeutics. Enhancing the release of endogenous cytokines is, however, an alternative approach. The imidazoquinolinamines imiquimod and resiquimod have demonstrated potency as inducers of IFN-α and other cytokines both *in vitro* and *in vivo*. Cytokine gene activation is mediated via the signal transducer and activator of transcription 1 (STAT-1) and involves the transcription factors NFκB and α4F1. Antiviral activity has been demonstrated against a variety of viruses, and clinical efficacy has been demonstrated against genital warts, herpes genitalis and molluscum contagiosum. Imiquimod is administered as a 5% cream (Aldara) and has been licensed for the treatment of anogenital warts in immunocompetent patients. Complete clearance of warts has been observed in up to half of treated patients with only local side effects reported. Resiquimod can be administered topically but also exists as an oral formulation. The range of potential infections for which these agents may have clinical utility includes chronic hepatitis C virus infection and Kaposi's sarcoma. In addition, the imidazoquinolinamines may find roles in the therapy of cancers and as vaccine adjuvants.

Significant advances in antiviral therapeutics have occurred in recent years. A number of agents that inhibit viral replication *in vitro* have been developed, including agents active against human immunodeficiency virus (HIV), cytomegalovirus (CMV) and herpes simplex virus (HSV). The initial promise of antiviral agents has been offset by the development of antiviral resistance in specific populations, such as immunocompromised hosts.[1] In addition, for many viruses effective antivirals are not available. An alternative strategy in antiviral therapeutics involves enhancing the host's natural immune response to viruses by the administration of exogenous cytokines. The cytokine that has demonstrated the greatest antiviral potential has been interferon-α (IFN-α), which is a component of therapy for chronic hepatitis C virus (HCV) hepatitis and shows efficacy against other viruses.[2] Therapy with cytokines is, however, parenteral and is associated with unwanted side-effects.

Imiquimod (Aldara, R-837, S-26308) and resiquimod (R-848, S-28463) are members of a new group of low molecular weight compounds, the imidazoquinolinamines[3] (Figure). These have been shown to have properties as immune response modifiers *in vitro* and *in vivo*, and demonstrate antiviral and anti-tumour activity via endogenous cytokine production.[3,4] *In vitro* studies using non-human or human monocytes treated with imiquimod or resiquimod have reported increased mRNA in cell lysates and/or cytokine levels in supernatants of IFN-α, interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α.[3,5–7] In comparison with lipopolysaccharide or viral stimulation, IFN-α fold induction was greater than that of other cytokines.[3,5–7] IL-1α, IL-1 receptor antagonist, IL-6, IL-8, IL-10, granulocyte-macrophage colony stimulating factor, granulocyte colony stimulating factor and macrophage inflammatory protein-1α were also upregulated.[3] Resiquimod is more potent at inducing cytokine expression than imiquimod. The clinical significance of many of these cytokines is uncertain due to the variable experimental conditions employed. *In vivo* studies of humans and animals treated with topical 5% imiquimod cream or topical 0.1–1.0% resiquimod gel have, however, confirmed the induction of

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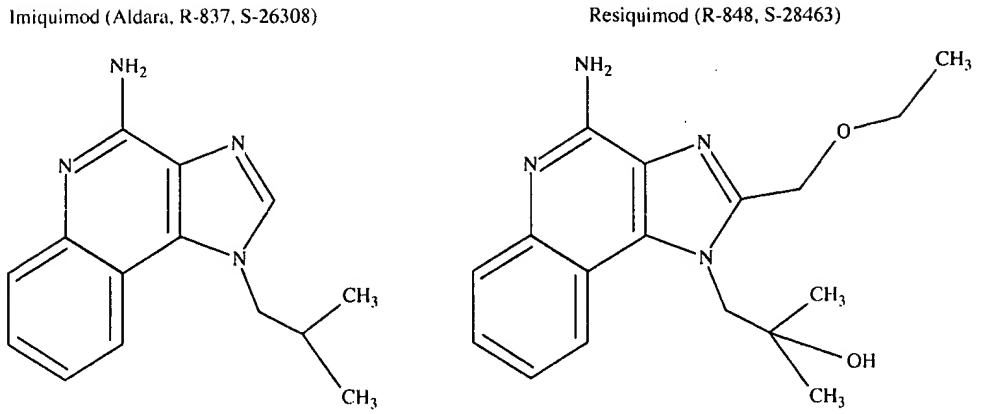

Figure. The chemical structures of imiquimod and resiquimod.

mRNA for IFN-α and TNF-α in treated but not untreated skin.[8,9] In addition to monocytes, keratinocytes in skin were stimulated to produce cytokines. Imiquimod upregulated IL-6 and IL-8 *in vitro*,[3] while resiquimod induced mRNA for IL-1α, IL-8, TNF-α and transiently IFN-α.[10]

Peripheral blood mononuclear cell cytokine induction by imiquimod *in vivo* required tyrosine and protein kinase C activity, was independent of cellular protein synthesis and was mediated via the transcription factors NFκB and α4F1.[11] Furthermore, mice lacking a component of the IFN-stimulated gene factor 3, termed the signal transducer and activator of transcription 1 (STAT-1), lacked imiquimod-mediated gene activation.[12] Patients responding to topical imiquimod treatment of genital warts had higher constitutive pretreatment levels of STAT-1.[13] Hence, imiquimod modulates IFN signal transduction to enhance transcription of IFN-α stimulated genes.

Langerhans' cells (LC), which are potent antigen-presenting cells in multiple locations including the skin, demonstrated functional activation and enhanced induction of T-lymphocyte proliferation in response to imiquimod or resiquimod treatment.[14] LC migration to draining lymph nodes was also enhanced, which could facilitate antigen presentation to T-lymphocytes.[15] A Th-1 cytokine profile, including IFN-γ, was preferentially induced in mitogen-stimulated T-lymphocytes exposed to imiquimod or resiquimod.[16] This was mediated by upregulation of IFN-α and IL-12 in monocytes and macrophages, an effect seen to a greater extent with resiquimod than with imiquimod treatment.[16] B-lymphocytes proliferated, became activated and were stimulated to produce immunoglobulin.[17] In these studies resiquimod was more potent at inducing lymphocyte proliferation and was also capable of aiding immunoglobulin class switching, unlike imiquimod.[17] These links between innate and acquired immune responses suggest the potential usefulness of imiquimod, and in particular, resiquimod, as agents that could enhance vaccine responses.

Imidazoquinolinamines demonstrate indirect antiviral activity *in vivo* owing to cytokine induction, which inhibits viral replication directly and stimulates innate and acquired antiviral immune responses. In patients treated with 5% imiquimod cream, human papillomavirus (HPV) DNA and mRNA for the L1 gene were significantly decreased in association with a clinical response to therapy.[8] Animal models, case reports and open-label studies have variously demonstrated the antiviral effect of imiquimod against HSV, Rift Valley fever virus, Banzi virus and in the treatment of molluscum contagiosum.[3,18,19] In most circumstances the observed antiviral effect has been associated with topical administration. The pharmacokinetics of topical administration are incompletely delineated but systemic absorption has not been detected, so the effect is local.[3] The cream is usually applied to clean dry skin and left for 6–10 h before being washed off.

Resiquimod has greater potency at inducing cytokine expression than imiquimod but whether this will increase its antiviral spectrum is presently unknown. It may, however, be more useful than imiquimod in treating HSV-2 and may also be used in HCV infection.[20,21] In a guinea-pig model of HSV-2 infection, resiquimod was effective when administered by dermal, subcutaneous or intravaginal routes before infection.[20] Antiviral activity is related to induction of serum 2′,5′-oligoadenylate synthetase activity. Resiquimod was also found to decrease recurrence of HSV-2 when administered subcutaneously in this model. Unlike imiquimod, for which pre-systemic biotransformation has limited its oral bioavailability, resiquimod may be administered by the oral route and trials are under way to assess its use in anti-HCV therapy, for which IFN-α forms the cornerstone of therapy.[21]

Imiquimod 5% cream (Aldara) is licensed for the treatment of anogenital warts in immunocompetent patients. The evidence supporting this license comes from three prospective, double-blind, randomized, vehicle-controlled trials.[22–24] In these trials 698 immunocompetent individuals were randomized to receive topical therapy with imi-

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quimod 5% cream, 1% cream ([22,23] only) or vehicle control. The topical treatment was applied daily[22] or three times a week[23,24] for 16 weeks or until lesions cleared. Complete clearance of warts was observed in 37–52% of those treated with 5% cream, 14–21% of those treated with 1% cream and 0–11% of those treated with vehicle control by intent-to-treat analyses.[22–24] For complete responders, relapse rates at 10–12 weeks were 13–19% for 5% cream, 0–17% for 1% cream and 0–10% for vehicle control. Response rates were higher in female as compared with male patients. Local skin effects, including erythema, excoriation, flaking and erosion, were common but usually well tolerated. Ulceration was also noted in a minority of patients. These side-effects were associated with itching, pain and burning but systemic side-effects were not reported as occurring with greater frequency in the treatment group.[22] None of these studies analysed changes in HPV DNA. Subsequent clinical audit has demonstrated a similar response rate.[25]

Therapy of anogenital warts in HIV-seropositive individuals has been less effective. In a randomized, double-blind, vehicle-controlled trial of imiquimod 5% cream administered three times a week in 100 HIV-seropositive individuals receiving antiretroviral therapy and with CD4 T-lymphocyte counts >100 $\times$ 10^6 cells/L, complete response rates were seen in only 11% of the imiquimod group, compared with 6% of the control group, after 16 weeks of therapy, a result that was not statistically significant.[26] A $\geq$50% reduction in wart size was, however, demonstrated in 38% of those who received imiquimod as compared with 14% of controls ($P = 0.01$), and the therapy was well tolerated. The number of individuals in this study whose HIV RNA plasma copy number was undetectable was not stated. Further studies are needed to address how this response rate can be improved.

In a further, double-blind, randomized, vehicle-controlled trial, 100 immunocompetent patients with molluscum contagiosum were randomized to receive a control or 1% imiquimod cream three times daily, 5 days a week for 4 weeks.[27] Clearance of lesions was demonstrated in 82% of the imiquimod-treated individuals but only 16% of controls. Relapse rates after 10 months of follow-up were very low.

Resiquimod may also find a role in the treatment of HPV or molluscum contagiosum infection. In addition, it may be particularly useful against HSV-2, either as an agent to prevent recurrence or as a vaccine adjuvant in the presence of HSV glycoproteins. In a randomized study involving 52 immunocompetent individuals with a history of six or more recurrences of herpes genitalis per year, resiquimod demonstrated clinical efficacy.[28] Resiquimod gel at various concentrations, or vehicle control, was administered to lesions within 24 h of onset and treatment continued for 3 weeks. The median time to first recurrence was 169 days for the combined resiquimod treatment group as compared with 57 days for the control group ($P < 0.01$). In the 6 months of follow-up 32% of the resiquimod but only 6% of the control group had no recurrences ($P < 0.05$). A European multicentre Phase III randomized double-blind study is currently determining the efficacy of 0.01% resiquimod gel at preventing recurrences of anogenital herpes.

It is likely that immune response modifiers similar to imiquimod and resiquimod will find other clinical indications but many questions remain to be answered. Imidazoquinolinamines may have efficacy in the treatment of conditions for which IFN-α is currently employed, such as Kaposi's sarcoma (KS) and chronic HCV infection. Cutaneous lesions such as HSV genital ulcers or KS lesions could be treated using the topical preparations already studied. However, conditions such as chronic HCV hepatitis would require an oral formulation and resiquimod may be better suited to these uses.[21] Interestingly, Phase I trials of an oral formulation of imiquimod have already been conducted in HIV-seropositive individuals and patients with cancer.[29] The potential role of oral imiquimod in the therapy of HIV infection is intriguing but caution is warranted; in this trial of oral imiquimod in HIV-seropositive individuals two of 10 (20%) individuals demonstrated dramatic increases in plasma HIV RNA copy number, while two individuals demonstrated significant decreases. Transcription factors critical for imiquimod-mediated cytokine induction, such as NFκB, also upregulate HIV replication, and the significance of LC migration to lymph nodes in HIV immunopathogenesis needs to be investigated. Imiquimod, and to a greater extent resiquimod, have also demonstrated leishmanicidal activity due to nitric oxide synthesis in macrophages in an animal model of cutaneous leishmaniasis, suggesting other potential uses of imidazoquinolinamines against infection.[30]

In addition to the therapy of established infection the imidazoquinolines may have activity in therapy of cancers such as basal cell carcinoma (BCC). Of 24 patients treated, at various dosing intervals, with topical 5% imiquimod cream, 20 (83%) lacked evidence of BCC on biopsy 6 weeks after therapy compared with only one of 11 (9%) of the group treated with vehicle control.[31] It remains to be established whether oral formulations of imidazoquinolines will extend the range of potential cancers that could be treated.

Furthermore, the role of imidazoquinolines as vaccine adjuvants requires investigation. Adjuvants are essential to enhance the efficacy of vaccination with weak immunogens. The development of safe and effective adjuvants to boost cell-mediated immunity is a priority of human vaccine research. Imidazoquinolines induce Th-1-mediated immune responses as opposed to the Th-2 responses associated with the use of alum, which is currently used as an adjuvant in human vaccines.[32] This is the result of IFN-α and IL-12 production, which enhances IFN-γ production. The potential advantages of inducing Th-1 responses in

response to immunization could have far-reaching consequences in the management of infections and cancer.

Many more studies are urgently needed to determine the safety and applicability of these novel immunomodulating agents in the therapy of HIV infection, other infectious diseases, cancer and in the development of immunization protocols. However, they are already demonstrating clinical utility in the therapy of genital warts, molluscum contagiosum and, potentially, herpes genitalis.

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